EPO Machine Translation of DE 101 44 557

The invention concerns formulations of medicament, which the connection:

EMI1.1
(5-Methyl-2-oxo-1,3-dioxolen-4-yl) methyl (5R, 6S) - 6 [(R) - 1-hydroxyethyl] - 7-oxo-3 [(R) - 2-tetrahydrofuryl] - 4-thia-1-aza-bicyclo [3,2,0] hept-2-ene-carboxylat)
or hydrates of it as active substance contained and the contained active substance controlled set free.
The connection belonged to the class of the beta lactam antibiotics and possesses the INN (international Non Proprietary name) Faropenemdaloxat and in the following thereby is designated. It described in EP-B-544 907 and EP-A-757 050.
After gift the concentrations of the active substance in the blood are subject to a fast setting free formulation of tablet with the repeated administration of the formulation of medicament strong fluctuations usual for the therapy. After by-oral application z. B. the maximum concentrations of the active substance in the blood can be achieved by formulations with fast active substance release fast. These drop then up to the next application very fast, in case of far open Ems amount to the radioactive half-life one hour (t< 1> /2 = h). Thus strong fluctuations of the concentrations of the active substance in the blood result in the case of repeated administration of formulations of tablet with fast active substance release. In case of of beta lactam antibiotics it is however desirable to maintain the concentrations of the active substance in the blood on a higher level during a longer period.
Such a formulation of medicament with controlled release can hold the active substance concentration in the blood not only during a longer period away on wished the constant level, but has a number of fundamental advantages to offer beyond that, like the smaller frequency of the administration, which leads to a better acceptance with the patient (so-called. Compliance), thus z. B. 1-2 daily gifts instead of 2-4mal daily as with fast-setting free formulations of standard. In particular advantages can be obtained compared with fast setting free formulations with certain infections, with which it depends on longer persisting active substance mirrors. Altogether a formulation of medicament with controlled release offers larger possibilities of co-ordinating the active substance mirror purposefully at the special infection and the situation of the patient.
There was therefore the desire for the development of a formulation of medicament for Faropenemdaloxat, which fulfills the requirements described before. The inventors examined therefore the absorption behavior of the Faropenemdaloxats in the Gastrointestinaltrakt first intensively and found completely surprising with the fact that, z. B. contrary to other beta - lactams of this also in the deep intestine sections (also in the Colon) one absorbs. This for beta - lactams surprising absorption behavior of the Faropenemdaloxats at all only the possibility, one opens controls setting free formulation to develop.
During its further intensive research it succeeded to develop formulations of medicament which set the active substance free during a longer period in the Gastrointestinaltrakt. Finally to overcome formulations of medicament with certain setting free profiles developed, which are suitable, the problems of the state of the art described above.

The subject of the invention is thus a formulation of medicament with controlled active substance release, which covers Faropenemdaloxat or hydrates of it, and which one release of 30-85% after 30 min and 50-100% exhibit after 2 h.
The subject of the invention is also a formulation of medicament with controlled active substance release, which covers Faropenemdaloxat or hydrates of it, and which one release of 50-85% after 30 min and 70-100% exhibit after 2 h.
The subject of the invention is also a formulation of medicament with controlled active substance release, which covers Faropenemdaloxat or hydrates of it, and which one release of 60-80% after 30 min and 80-100% exhibit after 2 h.
In order to obtain the above-mentioned setting free profiles, in an execution form of the invention Faropenemdaloxat is covered with a lacquer controlling the release or embedded into a polymer. The active substance is released by diffusion. This formulation can be present as tablet or granulates, which can be suspended if necessary in a suitable suspension medium of aqueous or oily nature.
In a further execution form the invention concerns formulations of medicament, which essentially consist of Faropenemdaloxat and are embedded with a lacquer controlling the release covered or into a polymer and which by diffusion release active substance. In a further execution form the invention concerns such a formulation of medicament, by the fact characterized that it concerns a tablet or granulates, which can be suspended if necessary in a suitable suspension medium of aqueous or oily nature.
Another possibility the above-mentioned setting free profiles to obtain, consists including of it the active substance into a matrix of a water-pourable polymer. The active substance is released in this case by erosion and diffusion. This formulation can likewise be present as tablet or granulates, which can be suspended if necessary in a suitable suspension medium of aqueous or oily nature.
In a further execution form the invention concerns a formulation of medicament, by the fact characterized that it covers the active substance in a matrix of a water-pourable polymer. In a further execution form the invention concerns such a formulation of medicament, by the fact characterized that it concerns a tablet or granulates, which can be suspended if necessary in a suitable suspension medium of aqueous or oily nature.
As water-pourable polymer z can. B. Hydroxypropylmethylcellulose or Hydroxypropylcellulose to be used. Hydroxypropylcellulose M. is particularly suitable.
In a further execution form the invention concerns a formulation of medicament, by the fact characterized that it concerns with the water-pourable polymer Hydroxypropylmethylcellulose or Hydroxypropylcellulose.
In a further execution form the invention concerns a formulation of medicament, by the fact characterized that it concerns with the water-pourable polymer Hydroxypropylcellulose M.
The above-mentioned formulations know additionally sweet means, antiadhesive, water-soluble polymers, and dispersing agents contain. In a particularly preferred form of the covered formulation it contains magnesium stearate, Hydroxypropylmethylcellulose of Faropenemdaloxat, Aspartam; Eudragit and Tween 20.
In a further execution form the invention concerns a formulation of medicament, by the fact characterized that it concerns a formulation of medicament, which contains sweet means, antiadhesives, water-soluble polymer, set free-controlling polymer and dispersion aid.

In a further execution form the invention concerns a formulation of medicament, by the fact characterized that it concerns a formulation of medicament, which contains Faropenemdaloxat, Aspartam, magnesium stearate, Hydroxypropylmethylcellulose, Eudragit and Tween 20.
An osmotic medicament setting free system represents a further possibility the above-mentioned setting free profiles to obtain. The osmotic setting free profile can consist of:

a) a core, which contains if necessary the active substance, if necessary a hydrophilic polymere source means and a water-soluble material for inducing of the osmose,
b) a covering from for water permeable and for the components of the wirkstoffhaltigen core an impermeable material,
c) an opening by the covering b) for the transport of the components contained in the core into the surrounding aqueous body fluid.

In a further execution form the invention concerns a formulation of medicament, by the fact characterized that it concerns an osmotic medicament setting free system.
In a further execution form the invention concerns a formulation of medicament, consisting of:

a) a core, which contains if necessary the active substance, if necessary a hydrophilic polymere source means and a water-soluble material for inducing of the osmose,
b) a covering from for water permeable and for the components of the wirkstoffhaltigen core an impermeable material,
c) an opening by the covering b) for the transport of the components contained in the core into the surrounding aqueous body fluid.

The received results of a pharmakokinetischen study show that with the available invention extended plasma concentrations above a border concentration [T > MHK] with same dose and lower maximum concentration were reached.
The received results show that with the available invention extended plasma concentrations above a border concentration [T > MHK] with same dose and lower maximum concentration were reached.
For the determination of the release in accordance with the definition of the invention the formulations of medicament of the available invention in the ?equipment 2? the USP XXIII are examined (The United States Pharmacopeia USP XXIV 1996, < 724>). As test medium 900 ml acetate buffers pH 4,5 with 0.5% Natriumlaurylsulfat one uses. The rotational speed of the agitator amounts to 75 revolutions per minute. Samples are pulled by 10 mu m a filter and their active substance content is determined. Those as dissolved certain active substance quantity is converted in this way into weight percentage of the assigned active substance quantity.
For the oral application here well-known formulations of medicament are suitable, like z. B. Tablets (not-covered as well as covered tablets, z. B. with gastric juice-resistant coats provided tablets or film tablets), caps, dragees, granulates, pellets, powders, emulsions, suspensions and solutions.

The active substances can be transferred in actually well-known way into the aforementioned application forms. This does not happen using inertly, pharmaceutical suitable auxiliary materials. For this count and. A. Carrier materials (z. B. microcrystalline cellulose, lactose), polymers (z. B. Celluloseether, Polyacrylsäuren, Polymethacrylsäuren or copolymers from Methacrylsäure and Methylmethacrylat and esters), explosive (z. B. Croscarmellose, sodium and transverseinterlaced Polyvinylpyrrolidon), flow regulating agent (z. B. hochdisperses silicon dioxide), lubricating and antiadhesive (z. B. Magnesium stearate), softener (z. B. Polyethylene glycol, tri ethyl CIT advice), solvent (z. B. liquid Polyethylenglycole), emulsifying agents (z. B. Natriumdodecylsulfat), thickener (z. B. Xanthangummi), dispersion aid (z. B. Tween 20), stabilizers (z. B. Antioxidantien such as ascorbic acid), coloring materials (z. B. inorganic pigments such as ferric oxides) or taste and/or Geruchskorrigentien.
Generally it proved as favourable to give with oral application quantities from approximately 30 to 800 mg, preferably about 150 to 600, in particular 300 to 600 mg Faropenem per single dose for achievement effective results whereby the treatment so long as necessary with the appropriate income frequency (z. B. bid, tid) one accomplishes. With children the quantity amounts to about 5 to 10 mg/kg, preferably about 7.5 mg/kg body weight.
Nevertheless it can be if necessary necessary to deviate from the quantities mentioned as a function of body weight, application way, individual behavior opposite the active substance, kind of the preparation and the time and/or. Interval, to which the application takes place.
The formulations of medicament according to invention with controlled active substance release can also as liquid medicine form, z. B. as suspended granulates, it is present whereby the suspension medium more aqueous or oily nature can be. Such a juice contains granulates particles, which essentially consist of Faropenemdaloxat and are embedded with a lacquer covered or into a polymer.
The attitude of the release defined above takes place here via purposeful attitude of the pores of the diffusion lacquer and its thickness. As Porenbildner soluble polymers can, like z. B. Polyethylenglycole, Polyvinylpyrrolidone, Hydroxypropylmethylcellulosen, Carboxymethylcellulosen or their salts, Methylcellulosen, Dextrine, Maltodextrine, Dextrane or other soluble compounds, like z. B. Salts (common salt, Kaliumchlorid, ammonium chloride etc.), urea, sugar (glucose, Saccharose, Fructose, lactose etc.), sugar alcohols (Mannit, Sorbit, Lactitol etc.) to be used. The portion of the Porenbildners of the quantity of enamel amounts to thereby 0 to 50% (GIG).
The erfrndungsgemässe granulates can be for example manufactured, by one gemahlenes Faropenemdaloxat with a middle particle size of 10-50 mu m during a fluidized bed process with an aqueous polymer dispersion from Eudragit NE 30D (Poly (ethylacrylat, methylmethacrylat) 2: 1) and Hydroxypropylmethylcellulose 3 cP covers and/or embeds.
In a further arrangement of the formulation of medicament with controlled active substance release of the available invention formulations are used, which cover the active substance in a matrix of a water-pourable polymer (formulations of hydraulic colloid matrix). These formulations can be present in form of granulates or in form of a tablet. That quantity of the matrix of the water-pourable polymer preferably is about 5 to 50 Gew %.

As water-soluble, hydraulic gel screen end of polymers prefers Hydroxypropylcellulosen (HPC), Hydroxypropylmethylcellulosen (HPMC), Methylcellulosen, Carboxymethylcellulose, Alginate, Galaktomannane, Polyacrylsäuren, Polymethacrylsäuren or copolymers from Methacrylsäure and Methylmethacrylat, Guar, agar, Pektin, Tragant, rubber arabicum, Xanthan and/or. Mixtures of these substances assigned.
The use of Hydroxypropylcellulosen and Hydroxypropylmethylcellulosen is particularly preferential. HPC-M in 2%iger solution has a viscosity of 150-400 mPa.s.
The formulation of medicament, which covers the active substance in a matrix of a water-pourable polymer, is manufactured, by one the active substance, which mixes polymer and suitable auxiliary and carrier materials (described as above) as well as usual Tablettierhilfsmittel (described as above) and directly tablettiert. Furthermore it is possible, the active substance, to granulate the water-pourable polymer and suitable carrier materials in the fluidized bed. The quantity and viscosity of the water-pourable polymer are selected in such a way that tablets or granulates with the setting free speeds described above result. If the granulates is processed still to the tablet, it is sieved, mixed and tablettiert with a lubricant, like for example magnesium stearate. The tablet is if necessary still painted.
In a further execution form of the formulation of medicament with controlled active substance release of the available invention it concerns an osmotic medicament setting free system. Such osmotic medicament setting free systems are in principle while stationary the technology admit and become z. B. in detail discussed in smelling pool of broadcasting corporations W. Baker, ?Osmotic Drug Delivery: A Review OF the patent Literature ", journal OF control LED release 35 (1995) 1-21. The formulation of medicament as osmotic medicament setting free system exists preferentially out

a) a core, which contains if necessary the active substance, if necessary a hydrophilic polymere source means and a water-soluble material for inducing of the osmose, and
b) for water permeable and for the components of the wirkstoffhaltigen core an impermeable covering
c) an opening by the covering b) for the transport of the components contained in the core into the surrounding body fluid.

This special osmotic medicament setting free system is in principle while stationary the technology described, for example in the DE-A-23 28,409 or the US-A-3 85,770. Concerning the materials for the covering the US-A-3 916,899 and US-A-3 977,404 purchase mentioned there on the EP-A-0 is taken 277,092 and.
Concerning suitable hydrophilic polymere source means is for example on in the EP-A-0 277,092 as well as the WHERE 96/40080 specified polymere source means referred. For example Ethylenoxidhomopolymerisate (Polyethylenglycol) with different polymerization degrees, which admit Polyox TM for example under the designation are, with molecular weights between 100.000 to 8.000.000 as well as Vinylpyrrolidon vinyl acetate copolymers as well as further in the USA 3,865,108, US-A-4 002,173 and US-A-4 of 207,893 water-pourable polymers mentioned can be used.

The formulations of tablet of the invention contained per single dose appropriately, related to Faropenem, 100 to 1000 mg, prefers 100 to 600 mg of the active substance.
Examples

Comparison example 1

A fast-setting free Faropenemtablette contains 418 mg of gemahlenes Faropenemdaloxat, corresponds to 300 mg free acid. Additionally to it it contains sodium, lactose, Hydroxypropylcellulose, magnesium stearate, Polyethylenglycol, Hydroxypropylmethylcellulose and titanium dioxide of Croscarmellose. The fast-setting free tablets are manufactured after standard techniques, like mechanical grinding, Wirbelschichtgranulation, Tablettierung and aqueous lacquer finish.
Example 1

Composition of the granulates
Table 1
EMI11.1

The formulation described in example 1 became by Aufsprühen of the polymer dispersion (inclusive other above-mentioned auxiliary materials) in a fluidized bed plant manufactured.
Setting free behavior

It is shown that the formulations of medicament from comparison example 1 and example exhibit the 1 following release in the test after USP XXIII (page 3).
Table 2
EMI12.1

Description of the clinical pharmakologischen study

In the context of a clinical pharmakologischen study 6 became and/or. 8 healthy male pro gangs in a randomized CROSS over Designs 418 mg Faropenem Daloxat (according to 300 mg Faropenem) as standard tablet with fast release (comparison example), or as granulates with controlled release (example 1) appliziert. The application took place in the morning on sober stomach after at least. 10stündigem chamfered. Before the application and at defined times thereafter (see table) ml blood was removed from the pro gangs 5. According to production of the plasma by means of a validated HPLC method the concentration at Faropenem was determined.
The following table shows the middle plasma concentration after gift of the standard tablet (comparison example) and/or. after gift of the granulates with modified release (example 1) in form of the geometrical average values of 6 and/or. 8 pro gangs.

EMI13.1

Kinetic parameters
Here mean:

AUC: Surface under the plasma concentration time curve from 0 to infinite
Cmax: Maximum Arzneistofflconzentration in the plasma
tmax: Time up to reaching the maximum medicine material concentration in the plasma
t1/2: terminal radioactive half-life
T > MIC: Time with plasma concentrations over the minimum inhibiting concentration, here computes with 1 mg/L

EMI14.1

Example 2

Hydrokolloidinatrix granulates
Composition
EMI14.2

The granulates was made by Aufsprühen of a Hydroxypropylcelluloselösung on a mixture of Faropenemdaloxat and Hydroxypropylcellulose in a fluidized bed plant.
Setting free behavior

It is shown that the formulations of medicament from example 2 exhibit the following release in the test after USP XXIII (page 3).

EMI15.1

1. Formulation of medicament with controlled active substance release, which covers Faropenemdaloxat or hydrates of it, and which a release of 30 - 85% after 30 min and 50-100% after 2 h exhibit.
2. Formulation of medicament according to requirement 1, which exhibits one release of 50-85% after 30 min and 70-100% after 2 h.
3. Formulation of medicament according to requirement 1, which exhibits one release of 60-80% after 30 min and 80-100% after 2 h.
4. Formulation of medicament according to requirement 1, which essentially consists of Faropenemdaloxat and is embedded with a lacquer covered or into a polymer and which active substance releases by diffusion.
5. Formulation of medicine according to requirement 4, by the fact characterized that it concerns a tablet or granulates, which can be suspended if necessary in a suitable suspension medium of aqueous or oily nature.
6. Formulation of medicament according to requirement 1, by the fact characterized that it covers the active substance in a matrix of a water-pourable polymer.
7. Formulation of medicament according to requirement 6, by the fact characterized that it concerns a tablet or granulates, which can be suspended if necessary in a suitable suspension medium of aqueous or oily nature.
5. Formulation of medicament according to requirement 3 or 4, by the fact characterized that it concerns with the water-pourable polymer Hydroxpropylmethylcellulose or Hydroxypropylcellulose.

9. Formulation of medicament according to requirement 8, by the fact characterized that it concerns with the water-pourable polymer Hydroxpropylmethylcellulose of the viscosity 3 cP.
10. Formulation of medicament according to requirement 9, by the fact characterized that it concerns with the water-pourable polymer Hydroxypropylcellulose M.
11. Formulation of medicament according to requirement 6 or 7, by the fact characterized that it concerns a formulation of medicament, which contains sweet means, antiadhesives, water-soluble polymer, set free-controlling polymer and dispersion aid.
12. Formulation of medicament according to requirement 11, by the fact characterized that it concerns a formulation of medicament, which contains Faropenemdaloxat, Aspartam, magnesium stearate, Hydroxpropylmethylcellulose, Eudragit and Tween 20.